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Deep-Vein Thrombosis and Coumarin Skin Necrosis Associated With a Factor V Inhibitor With Lupus-Like Features

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We report a 71-year-old man who developed deep-vein thrombosis after major surgery. Coumarin skin necrosis developed after starting oral anticoagulant therapy. An inhibitor to factor V (61 Bethesda units) with lupus-like features was found as well as a low protein C level. The occurrence of these very rare findings indicates that despite profound procoagulant inhibition (factor V inhibition and anticoagulant therapy), hypercoagulation can occur. Am. J. Hematol. 57:176–178, 1998. © 1998 Wiley-Liss, Inc.

Key words: factor V inhibitor; lupus anticoagulant; deep-vein thrombosis; coumarin skin necrosis; protein C

INTRODUCTION

Acquired factor V inhibitors are rare and have been associated with surgery, use of aminoglycoside antibiotics, blood transfusions, systemic infections, malignancies, and exposure to bovine thrombin contaminated with bovine factor V [1,2]. Coumarin skin necrosis affects 0.01 to 0.1% of patients, usually between the third and tenth day of coumarin treatment [3,4].

We report a patient, who developed deep-vein thrombosis after major surgery, for which anticoagulant therapy was started. Subsequently, coumarin skin necrosis developed. A factor V inhibitor with features of a lupus anticoagulant was found.

CASE REPORT

A 71-year-old man underwent operative tumor debulking of a right temporo-parietal astrocytoma grade IV. He had no history of haemorrhagic diathesis. Preoperative coagulation tests showed an APTT of 23.9 sec (normal 25–34 sec), a prothrombin time (PT) of 11.2 sec (normal 11–14 sec), fibrinogen 3.0 g/L (normal 2.0–4.5 g/L), Fibrinogen Degradation Products <10 μmol/ml, and platelets 288×10^9/L. No fibrin glue or thrombin was used peroperatively. The postoperative course was uneventful. Subcutanous unfractionated heparin was started preoperatively (5,000 U twice daily). Ten days postoperative, the APTT was 26.7 sec and PT 10.9 sec. On the 18th postoperative day, a thrombosis of the left popliteal vein developed, confirmed by ultrasound. Intravenous heparin and oral phenprocoumon (Marcoumar) was started. During the first 3 days, the APTT was within the therapeutic range (83–110 sec). On the fourth day, the patient developed a hemorrhagic bullous skin necrosis of the right upper leg, which became necrotic. On that same day the APTT had increased to 155 sec and the PT was 55.6 sec, while the INR was >7.5. Because the clinical picture was typical for coumarin necrosis, phenprocoumon was discontinued and 10 mg vitamin K was given intravenously. The coagulation parameters, however, did not correct. Two weeks after stopping all anticoagulant

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TABLE I. Coagulation Factor Assays in Patient Plasma

Test	Undiluted (%)	1/160 (%)	Normal values
Factor II	13	96	50–150
Factor V	<3	<3	50–150
Factor VII	4	80	50–150
Factor X	10	78	50–150

therapy, the PT was 59.4 and the APTT 159 sec, the INR >7.5, while the thrombin time was 14.0 sec (normal 9–14 sec) and fibrinogen was 6.2 g/L. Platelet count was 355 × 10^9/L. There was no hemorrhage. Two weeks later the patient's clinical condition worsened due to pneumonia with fever up to 40°C. Because of the bad prognosis, no further investigations were done and no therapy was given. A few days later the patient died. Autopsy was not allowed.

METHODS

The APTT, prothrombin time, and thrombin time were measured using Cephotest (Nycomed, Oslo, Norway), Thromborel S (Behringwerke AG, Marburg, Germany), and Thrombin Reagent (Fibriquik, Durham, NC), respectively, on an Electra 1000C coagulometer (MLA, Pleasantville, NY). Standard clotting assays of factors II, V, VII, and X were performed using deficient plasmas (Biopool, Burlington, Canada, and Organon Teknika Corporation, Durham, NC). For the detection of lupus anticoagulant, the diluted Russel viper venom time (DRVVT, Kordia, Leiden, The Netherlands) was used with a platelet neutralization procedure (PNP). Anticardiolipin antibodies were measured by ELISA.

The level of factor V inhibitor was determined according to the Bethesda method. Antithrombin activity, protein S and C antigen were measured as previously described [5,6]. Factor II and X antigen were assessed by Laurell assay. Factor V Leiden mutation was assessed by polymerase chain reaction as previously described [7]. All clotting tests were performed 2 weeks after stopping anticoagulant therapy.

RESULTS

The PT was prolonged to 59.4 sec and the APTT was 159 sec. The APTT only partially corrected to 116 sec after a 1:1 mixture of patient and normal plasma. The DRVVT ratio of patient/control was 3.49 (normal <1.1). With platelet neutralization procedure (PNP), the ratio shortened to 2.96. IgG anticardiolipin antibody was 26 U/ml, IgM 49 U/ml (normal <20). Factor II, V, VII, and X activity was markedly decreased (Table I). All factors but factor V corrected after dilution of the test sample up to 1/160. The titer of the factor V inhibitor was 61 BU/ml. The level of antithrombin was 88%, protein S antigen 109%, protein C antigen 72%, factor II antigen 134%, and factor X antigen 125%. The factor V Leiden mutation was not present.

DISCUSSION

The prolonged PT and APTT and the lack of correction of APTT with normal plasma raised suspicion of a circulating anticoagulant. The markedly decreased factor V level (<3%) did not, in contrast to the other extrinsic clotting factors, correct after dilution of the test sample. This is consistent with a specific factor V inhibitor. The patient had two risk factors for the development of an acquired factor V inhibitor: major surgery and malignancy. Even in combination with anticoagulant therapy, the factor V inhibitor induced no bleeding. This is in agreement with platelet-associated factor V being the active co-factor in the human prothrombinase complex [8] and the fact that platelet factor V is relatively inaccessible to the inhibitor [1].

The positive DRVV test, suggesting phospholipid dependency, and positive anticardiolipin antibodies could indicate a lupus anticoagulant (LA). LAs, however, may be difficult to differentiate from specific factor inhibitors. We consider it unlikely that two separate inhibitors developed at the same time, as no abnormalities were found peri-operatively. Therefore, this patient probably had one inhibitor with both anti-factor V and lupus-like features. This type of inhibitor has been described once before [9].

The combination of an acquired inhibitor of factor V, deep-vein thrombosis, and coumarin skin necrosis has not been reported before. There were several risk factors for the development of thrombosis: recent surgery, an astrocytoma, which is frequently associated (28%) with thromboembolism [10], immobility due to hemiparesis, and a low protein C level. Possibly, the lupus-like activity of the inhibitor has also contributed. The combination of thrombosis and a factor V inhibitor has been reported three times before [9,11,12].

A relatively low protein C level, as in our patient, increases the risk for coumarin skin necrosis, which is caused by a state of hypercoagulation, induced by a rapid decrease of protein C during the start phase of coumarin therapy [13]. Possibly, the lupus-like activity of the inhibitor also contributed to the hypercoagulable state, resulting in the coumarin necrosis.

This case indicates that, with profound procoagulant inhibition (factor V inhibition and anticoagulant therapy) hypercoagulation can occur, resulting in deep-vein thrombosis and coumarin necrosis.

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